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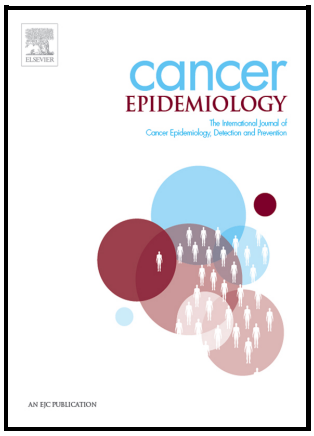


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PII: S1877-7821(22)00105-9

DOI: https://doi.org/10.1016/j.canep.2022.102200

Reference: CANEP102200

To appear in: *Cancer Epidemiology*

Received date: 9 March 2022
Revised date: 3 June 2022
Accepted date: 5 June 2022

Please cite this article as: Gisel Lorena Fattore, Natalia Silvana Aráoz Olivos, Jose Enrique Carrizo Olalla, Lara Gomez, Agustina Flamenco Marucco and María Paz Rojas Mena, Mortality of patients with cancer and SARS-CoV-2 infection: results from the Argentinean Network of Hospital-Based Cancer Registries, *Cancer Epidemiology,* (2022) doi:https://doi.org/10.1016/j.canep.2022.102200

# Mortality of patients with cancer and SARS-CoV-2 infection: results from the Argentinean Network of Hospital-Based Cancer Registries

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Abstract

Background:

Cancer is an important risk factors in patients with COVID-19. We aimed to describe the clinical and demographic characteristics associated with mortality in patients with cancer who were infected with SARS-CoV-2.

Methods

We conducted a retrospective longitudinal study of 1206 patients with confirmed SARS-CoV-2 infection and cancer diagnoses registered in the Argentinean Network of Hospital-Based Cancer Registries (RITA), from March 31, 2020 to January 31, 2021. Demographic and clinical characteristics between survivors and non-survivors were summarized using descriptive statistics. The primary endpoint was all-cause mortality within 30 days of COVID-19 diagnoses. Risk factors for mortality were identified by logistic regression models.

Results

1206 patients with cancer and confirmed SARS-CoV-2 infection were included, median age 54 years (IQR [interquartile range] 42–65); 38.9% aged 60 or older; 793(65.8 %) were female. 1101(91.3%) had solid tumors, 105(8.7%) had hematological malignancies. The most frequent solid tumor was breast (278, 23.1%), and the hematological one was lymphoma (59, 4.9%). Cervical cancer was more frequent in survivors, while lung cancer predominated in non-survivors. 275(22.8%) patients were diagnosed with cancer within the past year. A total of 129(10.7%) patients died within 30 days after COVID-19 diagnoses, with a case fatality rate of 15.2%(16/105) for hematologic malignancies and 10.3%(113/1101) for solid tumors. Multivariable regression analysis showed that age 60-79 (OR [odds ratio] 4.69, 95% CI [confidence interval] 2.72-9.70); p=0.001), age >=80 (OR 12.86, 95% CI 5.08-32.54; p<0.001), time since cancer diagnoses <1 year (OR 2.49, 95% CI 1.57-3.93, p<0.001) and 1-2 years (OR

2.20, 95% CI 1.36-3.57 p=0.001), and lung cancer (OR 4.35, 95% CI 2.02-9.36, p<0.001) were risk factors for death.

Conclusion

Patients with cancer and SARS-CoV-2 infection have an increased risk of death. The risk factors identified emphasize the need to develop specific strategies aimed at reduce the risk of dying from COVID-19.

Keywords: COVID-19, cancer, mortality, RITA, Argentina

## 1. Introduction

Since the beginning of the SARS-CoV-2 pandemic in Wuhan in December 2019, many studies have shown that the risk of morbidity and mortality from COVID-19 is not uniform among infected patients, but depends on individual characteristics, such as age and comorbidities. Cancer, a major burden of disease worldwide, also increases the risk of COVID-19 [1]. There is evidence that individuals living with cancer have an increased risk of contracting SARS-CoV-2 infection and developing the disease [1,2,3]. This can be explained because of their systemic immunosuppressive state caused by the disease itself or the anticancer treatments, due to an increased immune response to infection secondary to immunomodulatory drugs, [4,5], or to the frequent visits to hospitals [3]. In addition, cancer patients are often older and have one or more comorbidities [1], which put them at risk of worse serious outcomes, additional intensive care hospitalization [6], and eventually an increased risk of death.

Although there is evidence suggesting that all-cause mortality is higher in COVID-19 patients with cancer than those without cancer [2,7], mortality risk differs among cancer patients. Because of the physiological aging process, and the greater prevalence of comorbidities in older patients, age is a key determinant of the prognosis of COVID-19 patients [8]. Thus, cancer patients over 60 may have more risk of severe outcomes [5,6,9,10,11]. However, results of a retrospective cohort [12] and a large meta-analysis [13] found no increased risk of death in elderly people. Several studies have shown higher mortality from COVID-19 in patients with lung and hematological cancers [2,3,9,10,12,14,15]. This goes against the data from the Cancer Consortium (CCC19) registry database [5] and from a cohort of cancer inpatients admitted to the hospital of the Brazilian National Cancer Institute (INCA) [16], which

reported no increased risk of dying for leukemia patients. An increased risk for death was seen for cancer patients diagnosed <1 year before COVID-19 diagnosis [11,17]; for patients under cancer treatment in the last 3 to 12 months [17], and with recent chemotherapy [5,18]. By contrast, Robillotti and colleagues [6] found no increased risk of death among cancer patients treated with chemotherapy or surgery within 30 days before COVID-19 diagnosis. In summary, studies show heterogeneous results; several have small sample sizes, encompass a short period, or are based on hospitalized patients, which make it difficult to draw conclusions for a more general population.

In Argentina, studies evaluating COVID-19 mortality in cancer patients are scarce and involve a small sample size [19]. Greater knowledge about COVID-19 infection in cancer patients using local data is a priority for the management of these patients. Therefore, the present study aims to describe the clinical and demographic characteristics associated with mortality in a large group of patients with cancer who were infected with SARS-CoV-2.

## 2. Methods

This retrospective longitudinal study used data of cancer patients with confirmed SARS-CoV-2 infection between March 31, 2020, and January 31, 2021. Data on cancer were obtained from the Argentinean Network of Hospital-Based Cancer Registries, (*Registro Institutional de Tumores de Argentina* - RITA), dependent of the National Institute of Cancer (INC). RITA is a national registry system created in 2011 and implemented in several public hospitals across Argentina. The registry collects administration and clinical data on all cancer types in a standardized way, used for administration purpose and improvement the quality of care.

Data on all confirmed COVID-19 positive patients were extracted from the National Health Surveillance System (SNVS 2.0), a registry based on mandatory electronic reporting of notifiable events. Linkages were performed using the National Identity Document (DNI) and surname.

Patients eligible for inclusion were people aged sixteen years or older, diagnosed with between January 1, 2015, and January 31, 2021, and with laboratory-confirmed SARS-CoV-2 infection (n= 1880). Exclusions criteria was that SARS-CoV-2 diagnosis preceded the cancer diagnosis by at least 10 days or that tumor site was poorly defined or unknown. In cases of multiple primary tumors, we decided to exclude the first tumor diagnosed. (Figure 1). The vital status of each patient was reviewed 30 days after the diagnosis of SARS-CoV-2 infection. This information was provided by SNVS 2.0 and was confirmed or completed with RITA records.

All procedures were conducted in accordance with the Helsinki Declaration, the International Ethical Guidelines for Health-related Research Involving Humans (2016), and the Personal Data Protection Law N º 25,326, ant the resolution of the Ministry of Health of the Nation N º 1480/11. The study was approved by the Research Ethics Committee of the National Hospital Prof. Alejandro Posadas, under registration number 600 EUPeS0/22/CEIHP.

3. Data collection

We obtained information about demographic data, clinical manifestations, tumor characteristics, treatments, and vital status from electronic records. Any error in data consistency was corrected by contacting the registry. Duplicates tumor or COVID-19 event records were eliminated.

Information on demographic and tumor characteristics was obtained from RITA records. The variables analyzed were sex, age (categorized as < 40, 40-59, 60-79, and >=80 years old), time since cancer diagnosis (categorized as <1, 1-2, and >2 years), Eastern Cooperative Oncology Group (ECOG) performance status score at cancer diagnosis, cancer stage, cancer type (hematological and solid), and cancer histology. Cancer stage was defined as the early (I–II) or late (III-IV) for solid tumors at cancer diagnoses according to the TNM staging system. The staging of hematological malignancies was not considered because the recommended staging system is different. Histology was classified using the International Classification of Diseases for Oncology, Third Edition (ICD-O3). Tumor sites in the sample include breast (C50), cervix uteri (C53), corpus uteri (C54), colorectal (C18-C20), lung (C34), skin (C44), prostate (C61), urinary tract (C64-C68), testis (C62). Hematological cancer was classified using the morphological codes as follows: lymphoma (959-972), leukemia (980-994), and other hematological (973-976, 998). History of treatment was confined to the first treatment at the institution registering the case. Variables related to COVID-19 symptoms and clinical manifestations on SARS-CoV-2 diagnoses were obtained from the SNVS 2.0 mandatory notification form and included fever, dysgeusia, anosmia, cough, diarrhea, vomiting, pneumonia, respiratory insufficiency, dyspnea, headache, and myalgia.

Data on comorbidities were obtained from RITA records and SNVS 2.0 notification forms. They were grouped as cardiovascular, metabolic (which included diabetes and obesity), respiratory, neurological, chronic kidney, and chronic liver disease, immunosuppression, smoking and pregnancy. The amount of comorbidities was grouped as (0, 1-2, >=3).

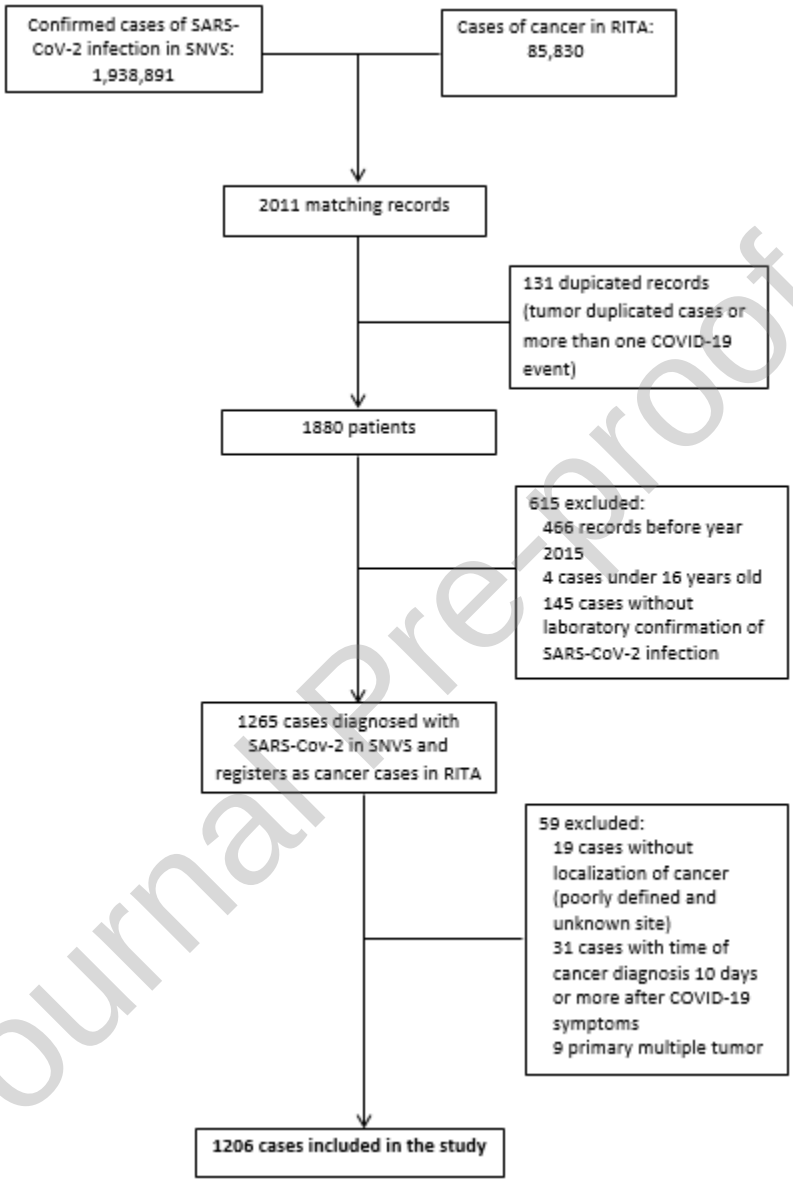
The primary endpoint was all-cause mortality, defined as the death among patients with cancer and COVID-19, within 30 days of diagnosis of COVID-19.

3.1 Statistical analysis

In this research we hypothesized that there were differences in demographic and clinical characteristics of patients with cancer history and SARS-CoV-2 infection between survivors and non-survivors. Quantitative variables were presented as medians (IQR), and qualitative variables were presented by frequencies and percentages (only available data were calculated). The median test, Fisher's exact test, $\chi^2$ test, were applied to analyze the differences between groups according to the type of data.

To explore potential risk factors associated with COVID-19 infection and cancer death, odds ratio (OR) and 95% confidence interval were analyzed by bivariate logistic regression. For the multivariable logistic regression analysis, we chose those variables with complete data and statistical significance from the bivariate logistic regression analysis ($p<0.05$). We also include interaction terms to evaluate the interaction between covariates on mortality risk. The tests we used were all two-sided with less than 5% type I error. The differences between groups were considered to be significant when the p-value was less than 0.05. We used IBM SPSS Statistics 21.0 software for statistical analysis.

Figure 1: Study profile





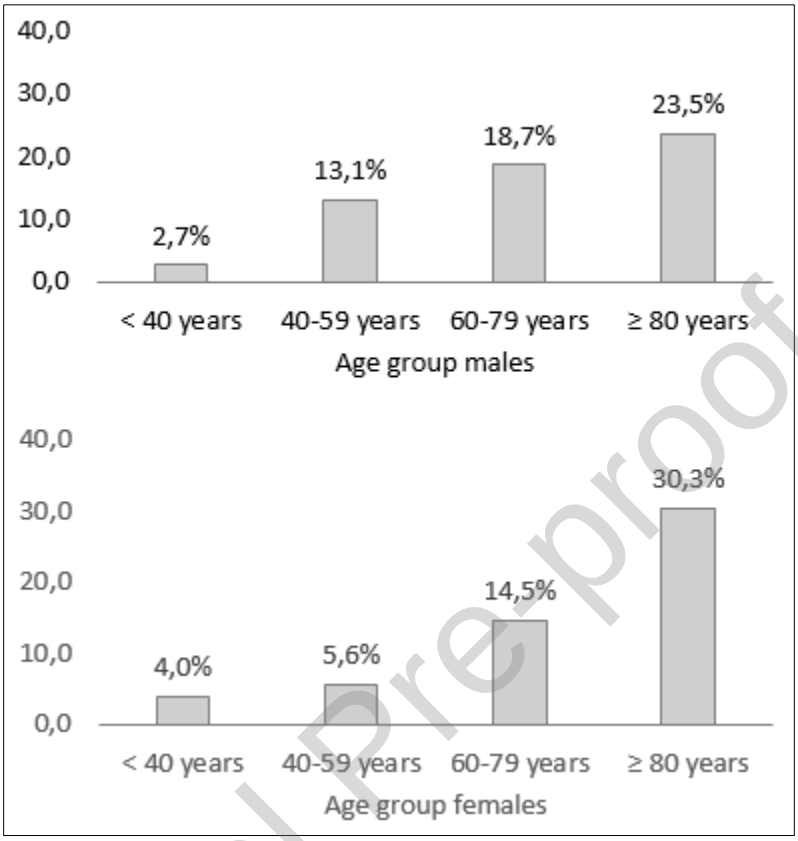

4. Results

4.1 Description of the population

From March 31 of 2020 to January 31 of 2021, 1880 patients with cancer registered in RITA were notified to the SNVS 2.0 with confirmed diagnoses of SARS-CoV-2 infection. Among these patients, 1209 met the criteria for inclusion and were enrolled in this study (Figure 1).

Demographic, clinical, and tumor characteristics for the analyzable population are in table 1. Of the 1209 patients with cancer included, 129 (10.7 %) had died as of March 03, 2021. 793 (65.8 %) patients were female, the median age was 54 years (IQR 42–65), and 470 (38.9%) patients were aged 60 or older, whereas in the non survivors group that age range represented a 64.4%. The case fatality rate increased with increasing age, reaching 23.5% in men and 30.3% in women aged 80 or older. (Figure 2).

Figure 2. Case fatality rate in patients with cancer and COVID-19 by sex and age group




The median time from cancer diagnosis to the onset of COVID-19 symptoms was 873 days (IQR 1463-395). 275(22.8%) patients had been diagnosed with cancer within the past year. Solid tumors were more frequent than hematological. The most prevalent solid tumor was breast (278, 23.1%) and cervical (228, 18.9%). Among hematological malignancies, lymphoma (59, 4.9%) and leukemia (27, 2.2%) predominated. Cervical cancer was more frequent in survivors, while lung cancer was more common in non-survivors.

Data of COVID-19 symptoms and clinical manifestation at SARS-CoV-2 diagnoses were available for 664 (55.0%) patients, the most common included were cough and fever, followed by headache, myalgia, and fatigue. Compared with survivors, non-survivors were more likely to

have dyspnea, chest pain, and pneumonia. Key symptoms for COVID-19 like anosmia, and dysgeusia were more common in survivors.

Also, comorbidities were available in 748 (62%) patients. 477 (63.8%) of them had 1 or 2 comorbidities besides cancer, and 94 (12.6%) had three or more. Cardiovascular disease was the most frequent, followed by metabolic and smoking history (Table 1).

Data of clinical stage was available for 453 (41.1%) of the 1101 solid tumors reported. Cancer stage I-II was the most frequent in our cohort (51.0%), while stage III-IV predominated in non-survivors (57.5%). Data on ECOG performance at cancer diagnoses was missing for 462 (38.3%) patients. There was no difference in ECOG scores between survivors and non-survivors. Regarding the history of treatment, data were available for 711 cases (58.9%), with surgery (44.0%) and chemotherapy (32.8%) the more frequent. History of chemotherapy seems to predominate in non-survivors (47.1%).

Table 1. Demographic and clinical characteristics in patients with cancer and COVID infection

| Variables | All patients (n= 1206) | Non-survivor (n=129) | Survivor (n=1077) | p-value |
|---|---|---|---|---|
| Sex | | | | 0.004 |
| Male | 413 (34.2%) | 59 (45.7%) | 354 (32.9%) | |
| Female | 793 (65.8%) | 70 (54.3%) | 723 (67.1%) | |
| Age (median, IQR) | 54 (42-65) | 64 (56-71) | 53 (41-64) | <0.001 |
| Age group, years | | | | <0.001 |
| < 40 | 249 (20.6%) | 9 (7.0%) | 240 (22.3%) | |
| 40-59 | 487 (40.4%) | 37 (28.7%) | 450 (41.8%) | |
| 60-79 | 420 (34.8%) | 69 (53.5%) | 351 (32.6%) | |
| ≥ 80 | 50 (4.1%) | 14 (10.9%) | 36 (3.3%) | |
| Cancer type | | | | 0.115 |
| Solid tumor | 1101 (91.3%) | 113 (87.6%) | 988 (91.7%) | |
| Hematological | 105 (8.7%) | 16 (12.4%) | 89 (8.3%) | |
| Tumor localization | | | | |
| **Solid tumor** | | | | |
| Breast | 278 (23.1%) | 25 (19.4%) | 253 (23.5%) | 0.295 |
| Cervical | 228 (18.9%) | 9 (7.0%) | 219 (20.3%) | <0.001 |
| Colorectal | 97 (8.0%) | 11 (8.5%) | 86 (8.0%) | 0.831 |
| Skin | 90 (7.5%) | 6 (4.7%) | 84 (7.8%) | 0.198 |
| Prostate | 44 (3.6%) | 2 (1.6%) | 42 (3.9%) | 0.221 |
| Kidney and urinary tractor | 37 (3.1%) | 7 (5.4%) | 30 (2.8%) | 0.105 |
| Testicle | 30 (2.5%) | 1 (0.8%) | 29 (2.7%) | 0.361 |
| Lung | 34 (2.8%) | 13 (10.1%) | 21 (1.9%) | <0.001 |
| Uterus body | 33 (2.7%) | 6 (4.7%) | 27 (2.5%) | 0.155 |
| Other solid† | 230 (19.1%) | 33 (25.6%) | 197 (18.3%) | 0.046 |
| **Hematological** | | | | |
| Lymphoma | 59 (4.9%) | 8 (6.2%) | 51 (6.2%) | 0.466 |
| Leukemia | 27 (2.2%) | 5 (3.9%) | 22 (2.0%) | 0.199 |
| Others of RES | 19 (1.6%) | 3 (2.3%) | 16 (1.5%) | 0.447 |
| Time since cancer diagnosis | | | | <0.001 |
| ≤ 1 year | 275 (22.8%) | 50 (38.8%) | 225 (20.9%) | |
| 1-2 year | 248 (20.6%) | 31 (24.0%) | 217 (20.1%) | |
| > 2 year | 683 (56.6%) | 48 (37.2%) | 635 (59.0%) | |
| Cancer Stage* | | | | 0.025 |
| In situ | 53/453 (11.7%) | 2/40 (5.0%) | 51/413 (12.3%) | |
| I-II | 231/453 (51.0%) | 15/40 (37.5%) | 21/413 (52.3%) | |
| III-IV | 169/453 (37.3%) | 23/40 (57.5%) | 146/413 (35.4%) | |
| Non information | 648 (58.9%) | 73 (64.6%) | 575 (58.2%) | 0.190 |
| ECOG performance status score* | | | | 0.011 |

| | | | | |
|---|---|---|---|---|
| 0 | 382/744 (51.3%) | 30/73 (41.1%) | 352/671 (52.5%) | |
| 1 | 307/744 (41.3%) | 32/73 (43.8%) | 275/671 (41.0%) | |
| 2 | 37/744 (5.0%) | 5/73 (6.8%) | 32/671 (4.8%) | |
| 3 | 16/744 (2.2%) | 5/73 (6.8%) | 11/671 (1.6%) | |
| 4 | 2/744 (0.3%) | 1/73 (1.4%) | 1/671 (0.1%) | |
| Non information | 462 (38.3%) | 56 (43.4%) | 406 (37.7%) | 0.207 |
| ECOG performance status score in last year* | | | | 0.071 |
| 0 | 87/162 (53.7%) | 11/26 (42.3%) | 76/136 (55.9%) | |
| 1 | 61/162 (37.7%) | 10/26 (38.5%) | 51/136 (37.5%) | |
| 2 | 5/162 (3.1%) | 3/26 (11.5%) | 2/136 (3.1%) | |
| 3 | 8/162 (4.9%) | 2/26 (7.7%) | 6/136 (4.9%) | |
| 4 | 1/162 (0.6%) | 0/26 (0%) | 1/136 (0.6%) | |
| Non information | 113 (41.1%) | 24 (48.0%) | 89 (39.6%) | 0.272 |
| Comorbidities* | | | | |
| Cardiovascular | 308/748 (41.2%) | 46/100 (46.0%) | 262/648 (40.4%) | 0.292 |
| Metabolic | 226/748 (30.1%) | 36/100 (36.0%) | 190/648 (29.3%) | 0.176 |
| Smoking | 216/748 (28.8%) | 32/100 (32.0%) | 188/648 (28.2%) | 0.439 |
| Respiratory | 73/748 (9.8%) | 15/100 (15.0%) | 58/648 (9.0%) | 0.058 |
| Immunosuppression | 50/748 (6.7%) | 7/100 (7.0%) | 43/648 (6.6%) | 0.892 |
| Renal | 46/748 (6.1%) | 10/100 (10.0%) | 36/648 (5.6%) | 0.085 |
| Neurological | 19/748 (2.5%) | 5/100 (5.0%) | 14/648 (2.2%) | 0.160 |
| Hepatic | 13/748 (1.7%) | 4/100 (4.0%) | 9/648 (1.4%) | 0.083 |
| Pregnancy | 5/748 (0.7%) | 1/100 (1.0%) | 4/648 (0.6%) | 0.513 |
| Non information | 458 (38.0%) | 29 (22.5%) | 429 (39.8%) | <0.001 |
| Number of comorbidities* | | | | 0.003 |
| 0 | 177/748 (23.7%) | 20/100 (20.0%) | 157/648 (24.2%) | |
| 1-2 | 477/7484 (63.8%) | 57/100 (57.0%) | 420/648 (64.8%) | |
| >3 | 94/748 (12.6%) | 23/100 (23.0%) | 71/648 (11.0%) | |
| COVID-19 manifestations* | | | | |
| Cough | 376/664 (56.6%) | 48/78 (61.5%) | 328/586 (56.0%) | 0.351 |
| Fever | 365/664 (55.0%) | 46/78 (59.0%) | 319/586 (54.4%) | 0.449 |
| Headache | 276/664 (41.6%) | 13/78 (16.7%) | 263/586 (44.9%) | <0.001 |
| Myalgia | 231/664 (34.8%) | 22/78 (28.2%) | 209/586 (35.7%) | 0.194 |
| General discomfort | 213/664 (32.1%) | 20/78 (25.6%) | 193/586 (32.9%) | 0.195 |
| Odynophagia | 210/664 (31.6%) | 10/78 (12.8%) | 200/586 (34.1%) | 0.001 |
| Anosmia | 133/664 (20.0%) | 2/78 (2.6%) | 131/586 (22.4%) | <0.001 |
| Dyspnea | 111/664 (16.7%) | 33/78 (42.3%) | 78/586 (13.3%) | <0.001 |
| Diarrhea | 93/664 (14.0%) | 10/78 (12.8%) | 83/586 (14.2%) | 0.748 |
| Dysgeusia | 84/664 (12.7%) | 3/78 (3.8%) | 81/586 (13.8%) | 0.013 |
| Arthralgia | 62/664 (9.3%) | 8/78 (10.3%) | 54/586 (9.2%) | 0.766 |
| Chest pain | 50/664 (7.5%) | 11/78 (14.1%) | 39/586 (6.7%) | 0.019 |
| Respiratory insufficiency | 48/664 (7.2%) | 16/78 (20.5%) | 32/586 (5.5%) | <0.001 |
| Vomiting | 44/664 (6.6%) | 7/78 (9.0%) | 37/586 (6.2%) | 0.375 |
| Abdominal pain | 31/664 (4.7%) | 5/78 (6.4%) | 26/586 (4.4%) | 0.395 |

| | | | | |
|---|---|---|---|---|
| Pneumonia | 31/664 (4.7%) | 8/78 (10.3%) | 23/586 (3.9%) | 0.021 |
| Non information | 543 (44.9%) | 47 (38.2%) | 496 (45.7%) | 0.115 |
| History of treatments* | | | | |
| Surgery | 313/711 (44.0%) | 28/70 (40.0%) | 285/641 (44.5%) | 0.475 |
| Chemotherapy | 233/711 (32.8%) | 33/70 (47.1%) | 200/641 (31.2%) | 0.007 |
| Radiotherapy | 91/711 (12.8%) | 5/70 (7.1%) | 86/641 (13.4%) | 0.136 |
| Hormonotherapy | 52/711 (7.3%) | 3/70 (4.3%) | 49/641 (7.6%) | 0.305 |
| Immunotherapy | 4 /711 (0.6%) | 0/70 (0%) | 4/641 (0.6%) | 1.000 |
| Others treatments | 18/711 (2.5%) | 1/70 (1.4%) | 17/641 (2.7%) | 1.000 |
| Non information | 495 (41.0%) | 59 (45.7%) | 436 (40.5%) | 0.252 |
| Treatments within 4 weeks before symptoms onset* | | | | |
| All | 23/700 (3.3%) | 7/69 (10.1%) | 16/631 (2.5%) | 0.005 |
| Surgery | 14/23 (60.9%) | 6/7 (85.7%) | 8/16 (50.0%) | 0.116 |
| Chemotherapy | 6/23 (26.1%) | 1/7 (14.3%) | 5/16 (31.3%) | 0.612 |
| Radiotherapy | 3/23 (13.0%) | 0/7 (0%) | 3/16 (18.8%) | 0.526 |
| Treatments within last year before symptoms onset* | | | | |
| All | 159/700 (22.7%) | 30/69 (43.5%) | 129/631 (20.4%) | <0.001 |
| Surgery | 77/159 (48.4%) | 13/30 (43.3%) | 64/129 (49.6%) | 0.535 |
| Chemotherapy | 57/159 (35.8%) | 14/30 (46.7%) | 43/129 (33.3%) | 0.170 |
| Radiotherapy | 13/159 (8.2%) | 1/30 (3.3%) | 12/129 (9.3%) | 0.465 |
| Hormonotherapy | 8/159 (5.0%) | 1/30 (3.3%) | 7/129 (5.4%) | 1.000 |
| Others treatments | 4/159 (2.5%) | 1/30 (3.3%) | 3/129 (2.3%) | 0.571 |

Data are n (%) or IQR= interquartile rate. RES= reticular endothelial system.† Other solids: thyroid, brain, stomach, ovary, melanoma, bladder, pancreas, unspecified uterus, soft tissue malignant tumor liver and intrahepatic bile ducts, larynx, gallbladder and intrahepatic bile ducts, bone, esophagus, other thoracic organs, anus, nostril, sinuses, middle ear, mouth, parotid, salivary glands, tongue, amygdala, other malignant tumors of the female genitalia, nasopharynx, oropharynx, pharynx and poorly defined lip and mouth, small intestine, other digestives, eye, penis. *Over available data.



We also compared the demographic, clinical and tumor characteristics between patients with solid and hematological cancer (Supplementary material). Case fatality rate was higher in patients with hematological malignancies (15.2%) than in those with solid tumors (10.3%), although the difference was not statistically significant. Patients with solid tumor were more frequently females (751/1101, 68.2%), while hematological malignancies predominated in males (63/105, 60.0%). Cardiovascular history was more frequent in patients with solid tumors

than in those with hematological malignancies (294/680, 43.2% vs 14/68, 20.6%), as well as metabolic history (214/680, 31.5% vs 12/68, 17.6%).

Conversely, immunosuppression history predominated in hematological malignancies (13/68, 19.1% vs 37/680, 5.4%). From 666 patients with solid tumor and information about treatment, 313 (44.0%) had history of surgery, while 42 (93.3%) of 45 with hematological malignancies had history of chemotherapy. Regarding history of treatment within last year before the onset of COVID-19 symptoms, 77 (52.0%) of 148 patients with solid tumor had surgery compared with none of patients with hematological malignancies, and 11 (100%) of patients with hematological malignancies received chemotherapy compared with 46 (31.1%) of 148 with solid tumors.

The association of demographic and clinical factors with death among patients with cancer and COVID-19 is summarized in table 2. We found that male sex, age older than 40, type of cancer (lung cancer), and time since cancer diagnoses (less than two years) increased the risk of death, while cancer stage, number of comorbidities, respiratory symptoms and ECOG performance status did not show statistical significance.

Those statistically significant variables with completed data were included in the multivariable regression analysis (Table 2).



Table 2. Logistic regression models. Risk factors associated with death in cancer patients with SARS-CoV-2 infection (n=1206)

| Variables | Univariable OR (IC95%) | p value | Multivariable OR (IC95%) | p value |
|---|---|---|---|---|
| Sex | | | | |
| Female | 1 (Ref) | … | … | … |
| Male | 1.72 (1.19-2.49) | 0.004 | 1.34 (0.89-1.98) | 0.152 |

| | | | | |
|---|---|---|---|---|
| Age range, years | | | | |
| ≤ 40 | 1 (Ref) | … | … | … |
| 40-59 | 2.19 (1.04-4.62) | 0.049 | 2.13 (1.01-4.53) | 0.054 |
| 60-79 | 5.24 (2.57-10.70) | <0.001 | 4.69 (2.72-9.70) | <0.001 |
| > 80 | 10.37 (4.18-25.70) | <0.001 | 12.86 (5.08-32.54) | <0.001 |
| Time since cancer diagnosis | | | | |
| >2 years | 1 (Ref) | … | … | … |
| 1-2 years | 1.89 (1.17-3.04) | 0.009 | 2.20 (1.36-3.57) | 0.001 |
| ≤1 year | 2.94 (1.92-4.49) | <0.001 | 2.49 (1.57-3.93) | <0.001 |
| Tumor localization | | | | |
| Other cancer | 1 (Ref) | … | … | … |
| Lung | 5.63 (2.75-11.55) | <0.001 | 4.35 (2.02-9.36) | <0.001 |
| Cancer stage | | | | |
| In situ | 1 (Ref) | … | | |
| I-II | 1.77 (0.39-7.99) | 0.457 | | |
| III-IV | 4.02 (0.91-17.64) | 0.065 | | |
| Number of comorbidities | | | | |
| 0 | 1 (Ref) | … | | |
| 1-2 | 1.07 (0.62-1.83) | 0.819 | | |
| >3 | 2.54 (1.31-4.93) | 0.006 | | |
| Symptoms | | | | |
| Dyspnea | 4.78 (2.87-7.94) | <0.001 | | |
| Respiratory | 4.47 (2.32-8.60) | <0.001 | | |
| insufficiency | 2.30 (1.13-4.71) | 0.022 | | |
| Chest pain | 2.80 (1.21-6.49) | 0.017 | | |
| Pneumonia | 0.09 (0.02-0.38) | 0.001 | | |
| Anosmia | 0.25 (0.08-0.81) | 0.021 | | |
| Disgeusia | 0.28 (0.14-0.56) | <0.001 | | |
| Odynophagia | 0.25 (0.13-0.45) | <0.001 | | |
| Headache | | | | |
| ECOG performance status score | | | | |
| 0 | 1 (Ref) | … | | |
| 1 | 1.37 (0.81-2.30) | 0.243 | | |
| 2 | 1.83 (0.66-5.05) | 0.241 | | |
| 3 | 5.33 (1.73-16.36) | 0.003 | | |
| 4 | 11.73 (0.72-192.33) | 0.084 | | |
| Chemotherapy | | | | |
| No | 1(Ref) | … | | |
| Yes | 1.97 (1.19-3.24) | 0.008 | | |

We found that age 60-79 (OR 4.69 [95% CI 2.72-9.70]; p=0.001) and >= 80 (OR 12.86 [95% CI 5.08-32.54]; p<0.001), time since cancer diagnoses less than 1 year (OR 2.49 [95% CI 1.57-3.93] p<0.001) and 1-2 years (OR 2.20 [95% CI 1.36-3.57] p=0.001), and lung cancer (OR 4.35 [95% CI

2.02-9.36] p<0.001) were associated with increased odds of death. There was no interaction effect between the selected variables (Supplementary material).

## 5. Discussion

To our knowledge, this is the first large report describing the clinical features and risk factors for mortality among patients with cancer diagnosed with SARS-Cov-2 in Argentina during the first year of the pandemic. Here, by integrating data from cancer registries (RITA, INC) with data on COVID-19 from the national surveillance system (SNVS 2.0), we find that patients with cancer are at higher risk of mortality once diagnosed with COVID-19. Furthermore, the risk for dying is greater in patients older than 60 years, when the time since cancer diagnoses is less than one and two years, and in those with lung cancer, but not with hematological malignancies.

Our findings show an overall case fatality rate (CFR) of 10.2%, nearly four-fold higher than the CFR observed in the Argentine population (2.7%) [20], and similar to those reported by a Brazilian cancer center (12.4%) [9], by the Cancer Consortium database (CCC19) (13 %) [5], and by the PRE-COVID-19 study (10 %) [21]. In contrast, it is quite less than the observed in Hubei (20%) [12], and by the UK Coronavirus Cancer Monitoring Project (UKCCMP) (28%) [22]. Reasons for these findings are unclear, but these two studies are based on hospitalized patients, enrolling more severe cases. Patients from the UKCCMP tend to be older, with a greater probability to require hospitalization and having adverse events. Conversely, our CFR is considerably higher than that found by Williams [23], who used the infection fatality rate (IFR) in order to correct for the ascertainment bias (when only more ill patients are tested for the disease).

Our data demonstrates that the risk of death in patients with cancer and COVID-19 increases substantially with age. This result is consistent with previous studies that pointed to age as a key determinant of the prognosis among patients with COVID-19 and cancer [5,6,9,10,11,22]. Early report from China did not find significant differences in age between survivors and non-survivors, probably because the study already comprised an elderly population [12]. Interestingly, in comparison with the general population, elderly patients with cancer may not be at increased risk of death when infected with COVID-19 [13], which implies that the presence of cancer may not further increase the already poor prognosis among the elderly people.

As other studies point out, mortality is significantly affected by the types of tumors [2,3,9,10,12,14,15]. From our analysis, patients with lung cancer have the highest death rates among all patients. Decreased lung function and severe infection in patients may contribute to the worse outcome in this subgroup [2]. As other studies have shown [5, 16] we did not find increased risk of death in patients with leukemia or other hematological malignancies. Patients with hematologic cancer, especially leukemia and myeloma, are more often treated with more myelosuppressive therapy and are severely immunocompromised because of underlying disease, so they may potentially be more susceptible to cytokine-mediated inflammation [10]. Despite we found a difference in CFR in favor of hematological tumors, our study did not have enough power to show statistical significance. Also, these results reflect the pattern of the lethality of these cancers in Argentina. The percent annual mortality (ratio of annual deaths/new diagnosis) is the highest for lung cancer (88.6%) and is also high for hematological malignancies (55.8%) [24], suggesting that COVID-19 infection may increase the mortality risk

associated with the type of cancer itself. Consistent with other studies [11,17,23], we observed an increased risk of death for patients recently diagnosed with cancer, which supports the fact that patients with active or progressive disease, as they have increased levels of immunosuppression (intrinsic or by cancer treatment), have a worse outcome [5].

The strengths of this study include sample size, study length and database linkage. The use of COVID-19 data from the National Health Surveillance System allowed us to match laboratory-confirmed SARS-CoV-2 cases from our cancer registry over a sustained period of time and obtain a considerable number of cases for analysis. During this period several peak stages occurred, which determined the availability of hospital technical and human resources, as well as the ICU ventilation capacity that could have affected the risk of mortality [25]. We use laboratory-confirmed cases to avoid possible confounding by other infections. However, it depends on the sensitivity of the PCR diagnostic test, and it is likely that the number of cancer patients affected with COVID has been underestimated [21]. Also, reported cases vary depending on the availability of testing, and it is expected that patients with mild disease or asymptomatic had not been tested and are, therefore, not included in this study. Other limitations include the incomplete documentation for many variables of interest, which does not allow us to evaluate the effect of treatment, comorbidities, and other measures of severity of disease such as hospitalization or need for intensive care.

During the first year of the pandemic, isolation measures in Argentina were strict, and professional societies discouraged unnecessary visits to hospitals to prevent cancer patients from developing COVID. In turn, changes in cancer service provision could have caused delays in

admission for treatment, and a reduction in early cancer diagnosis, which might result in excess deaths from cancer in the future [26].

## 6. Conclusions

In conclusion, patients with cancer who develop COVID-19 have an increased risk of death. Clinicians may pay special attention to those subgroups of cancer patients that showed a major vulnerability, such as those over 60 years of age, with lung cancer, and recently diagnosed. The risk factors identified emphasize the need to develop specific strategies aimed at reduce the risk of dying from COVID-19. Also, important efforts should be made to improve the quality of cancer registries.



## Acknowledgements

We thank all registrars involved in data collection and registration in RITA, and Antonia Rodríguez (National Program for the Prevention and Early Detection of Colorectal Cancer, National Cancer Institute) who provided language help.

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**Gisel Fattore**: Project administration, Conception and study design, Methodology, Interpretation of data, Writing- Original draft preparation. **Natalia Araoz Olivos**: Methodology, Formal analysis and interpretation of data, Writing- Reviewing and Editing. **José Carrizo**: Interpretation of data, Writing- Reviewing and Editing, Visualization. **Lara Gomez**: Conception and study design, Data collection, Writing- Reviewing and Editing. **Agustina Flamenco Marucco**: Data collection, Formal analysis and interpretation of

data, Writing- Reviewing and Editing. **María Paz Rojas Mena**: Data collection, Formal analysis and interpretation of data, Writing - Review & Editing

Highlights

- Elderly cancer patients are at increased risk of death when infected with COVID-19
- Case fatality rate is high for patients with lung cancer and COVID-19
- Mortality is higher for patients with COVID-19 and cancer recently diagnosed